

REMARKS

Claim 1 has been amended to limit the condition being treated to cognitive dysfunction and the compounds used to those having nicotinic effects. New claim 40 is directed to the same subject matter as claim 1 but limited to the preferred class of nicotinic allosteric potentiators

The examiner's first rejection under 35 USC 112 is not understood. As pointed out in response to the previous action, support for an amendment to exclude those diagnosed as suffering from Alzheimer's disease is found in paragraph 8 of the specification where it is reported that some compounds of the type specified in the claims have been used for treatment of Alzheimer's disease. The examiner makes no comment on the remarks made by the Applicant on this issue and so it is difficult to guess the basis for the examiner's concern. As pointed out previously, it is clear that the applicant did not wish to try to reclaim treatment for Alzheimer's disease in the present application. The present invention is totally distinct from treatment of Alzheimer's disease but because there is a possibility that the same person might be suffering from both conditions, the claims have been amended so as to simplify making a determination of patients falling within the specified group. Treatment for Alzheimer's disease as acknowledged as being prior art necessarily involves making a diagnosis of that condition. Defining the excluded group as those who have been so-diagnosed is therefore disclosed in the application as filed and is a more clear-cut definition than simply excluding those who are "being treated for Alzheimer's disease". If the examiner would prefer the latter language, however, the applicant would be willing to adopt it.

So far as the 35 USC 112 paragraph 1 rejection relating to the definition of the active compounds is concerned, the independent claims have been amended to limit these to nicotinic allosteric potentiators (which the examiner agrees are enabled) and nicotinic agonists. Such compounds have similar properties of nicotinic stimulation to nicotinic allosteric potentiators. The examiner gives no reason to distinguish between different types of nicotinic stimulation. Allosteric potentiation is one way to do this but the applicant should not be required to limit her claims to one particular means for implementing her invention when one skilled in the art would recognize alternative ways of effecting similar results. Forget nicotine All acetylcholinesterase inhibitors also have an indirect nicotinic stimulation

properties by increasing the supply of acetyl choline which has a nicotinic effect. However, in the interests of expediting prosecution of the present application, the applicant is willing to delete this broad class of compounds from the claim. It should, however, be noted that some acetylcholinesterase inhibitors, such as galanthamine also act directly as nicotinic allosteric potentiators. Such dual-function compounds remain within the scope of the claim by virtue of their nicotinic allosteric potentiation properties.

It is therefore submitted that the requirements of 35 USC 112 first paragraph have been complied with.

Turning now to 35 USC 112 second paragraph, claim 1 has been amended to make it clear that what is being treated is cognitive dysfunction associated with low LDL cholesterol values so that all that is required is a determination of cognitive dysfunction and low LDL cholesterol values and that there is no need to show that there is a causal link between the two in order to determine whether a patient does or does not fall within the scope of the claims. Those skilled in the art know how to determine whether cognitive dysfunction is present in a patient. The Muldoon article in Am. J. Med. 117: 823 - 829 submitted with our response of January 10, 2006 (a fresh copy of which is enclosed for convenience) enumerates a number of tests used to assess cognitive dysfunction (see the appendix), such as the Elithorn Mazes test and the Recurrent Words Test.

It is submitted that the claims are clear and that the requirements of 35 USC 112 second paragraph have been met.

So far as the 35 USC 103 rejection is concerned, the claims exclude treatment of patients who have been diagnosed as suffering from Alzheimer's disease. Since the examiner's rejection is predicated on the idea that those who suffer from Alzheimer's may also take statins and on the now no-longer accepted idea that taking statins may reduce the risk of Alzheimer's disease, it is submitted that it is no longer relevant to the claims as amended.

In response to the previous action, the applicant pointed out that the articles by Kivipelto and Simons teach away from the present invention. Galanthamine is known for the treatment of Alzheimer's disease. Kivipolto teaches that there is some correlation between elevated cholesterol values (no distinction was made between total cholesterol and low LDL-cholesterol) and Alzheimer's disease. Based on this teaching there would be no motivation to administer an Alzheimer's drug to patients with low cholesterol values. It would be those with high cholesterol values who would be expected to be suitable for treatment in this way. Similar comments apply with respect to the Simons article. Simons reports that studies indicate that lowering of cholesterol reduces the incidence of Alzheimer's disease. Based on this again there would be no reason to administer an Alzheimer's drug to patients having low LDL-cholesterol. Again, the examiner makes no comments on these arguments which places the Applicant in a difficulty in trying to guess the reason why they were not found persuasive.

Table 1 of the Kivipelto reference illustrates characteristics of the study population at baseline and in 1998 when re-assessment was done. It should be noted that differences in body mass index, systolic blood pressure and cholesterol, which were present at baseline, have disappeared by the re-examination. AD patients had weighed 1.1 kg more, but the weights were identical 21 years later. Systolic blood pressure had been 6.8 points higher in the AD group, but was 1.1 point lower at follow-up (not significant). Cholesterol had been 0.5 mmol higher (about 20 mg/dl), but was only 0.2 mmol higher (about 8 mg/dl) at re-exam (not significant). Thus, from these data, it seems that the *lowering* of cholesterol which occurred between the baseline and the demented state could equally well have contributed to the development of Alzheimer's disease.

The Kivipelto data could just as well have been analyzed by the retrospective prevalence methods in the papers cited by Simons . According to Table 3, 10 of 48 Alzheimer patients, and 208 of 1352 nondemented patients were receiving cholesterol-lowering drug treatment. Thus, among the 218 individuals on cholesterol medication, 10, or 4.6% had Alzheimer's disease. Among the 1182 untreated subjects, 38 had AD, for a prevalence of 3.2%. Because the prevalence of AD in patients on cholesterol-lowering medications, 4.6%, was certainly not lower than that in patients not on such drugs, 3.2%, the data could indicate that cholesterol-lowering has no preventive effect on the development of

Alzheimer's disease.

The Simons et al reference describes two retrospective studies. Jick et al (Lancet 2000; 356:1627-31) and Wolozin et al (Arch Neurol 2000; 57:1439-1443) [copies of both which are attached], for their citation of reduction of AD by statins. These studies have internal inconsistencies, were not regarded as reliable at the time, and the hypothesis they generated, that statin treatment prevents dementia, has since been disproven in prospective studies.

Jick et al analyzed a database of general practices in the UK, identifying 284 cases of dementia and 1080 controls matched for age, sex, index date, practice and time in the database. As shown in Table 2, the relative risk of dementia in patients with I see a space but no table appears.

Exposure	Cases	Controls	Adjusted relative risk estimate (95% CI)	p value
None, normal lipids	218 (76.8)	746 (69.1)	1.0	..
Hyperlipidaemia alone (no drug treatment)	29 (10.2)	142 (13.2)	0.72 (0.45-1.14)	0.16
Current use of statins	12 (4.2)	100 (9.3)	0.29 (0.13-0.63)	..
Current use of statins and other LLA	1 (0.4)	4 (0.4)
Past use of statins	0 (0.0)	14 (1.3)
Current use of other LLA	11 (3.9)	42 (3.9)	0.96 (0.47-1.97)	0.91
Past use of other LLA	13 (4.6)	32 (3.0)	1.31 (0.66-2.61)	0.44

*Adjusted for body mass index, smoking, hypertension, previous history of coronary-artery disease, coronary-artery bypass surgery, diabetes mellitus, and transient cerebral ischaemia.

Table 2: Adjusted risk ratio estimates for various exposures compared with non-exposed and hyperlipidaemia

untreated hyperlipidemia was 0.72; when treated with non-statin lipid-lowering agents, 0.96, and in statin-treated patients, 0.29. It did not differ among the individual statins prescribed: pravastatin, simvastatin and atorvastatin.

These data do not provide clinical support for the preclinical data indicating that cholesterol can promote cellular mechanisms of AD. As compared to patients with normal cholesterol values, patients with hyperlipidemia did not have an elevated incidence of dementia (most of which, in adults, is AD), whether treated with non-statin lipid-lowering agents, or untreated.

The absence of effect of cholesterol-lowering medications on the development of dementia is consistent with the data of Kivipelto, cited above. Only in the statin group was the dementia incidence significantly decreased (a finding which depends on 12 patients in the entire cohort of 1364 people). Because cholesterol levels or their alteration did not affect the risk of dementia, the question arises as to what other factors might have led to statin prescription, and been associated with a reduced incidence of dementia. The authors suggest "level of education, socioeconomic status and cholesterol, which themselves may be linked to the risk of dementia." (page 1629, upper right). At the time these data were collected, 1992 to 1998, statins were not as widely prescribed as they are now, nor had the National Cholesterol Education Program established the current laboratory standards, and non-medical factors may have played a role in prescribing decisions. Thus, the data in Jick et al are not supportive of cholesterol promotion of dementing processes, and any preventive effect of statins is open to some question.

The Wolzlin paper is similar. Three large hospital databases were combined in the Wolozin study. Patients taking each of three statins, pravastatin, simvastatin and lovastatin were compared to patients taking a series of cardiovascular medications, predominantly used as antihypertensives.

The prevalence of diagnosed AD (noted to include dementia with confounding vascular disease, page 1440, right side, end of first paragraph) was lower in patients on lovastatin and pravastatin than in those on simvastatin or a series of beta blockers, an ACE-inhibitor, or the diuretic furosemide. This is said to indicate that statins have an anti-dementia effect. There are several problems with this conclusion.

The first is that the non-statin drugs are, with the exception of furosemide, are used largely as antihypertensives. Hypertensives are at risk for vascular dementia as well as AD. Thus, the comparison group is enriched for patients with an elevated dementia risk and differences between the statin-users and those on cardiovascular medications may reflect the underlying diseases rather than the treatments.

Secondly, simvastatin does not show the preventive effect that pravastatin does. Wolozin et al comment that "Simvastatin and pravastatin are similar in structure, are equally

effective at inhibiting liver HMG-CoA reductase, and share similar blood-brain barrier permeabilities." The reference cited for this fact, instead, indicates that simvastatin enters the CNS and pravastatin principally does not.

Thus, simvastatin, which enters the brain, was not associated with a reduced incidence of AD, while pravastatin, which does not to a significant extent, was effective. In the Jick study, there was no difference between the effects of the two. The differential effects of pravastatin and simvastatin thus raise questions about the role of the statins in the differential prevalence of dementia.

A final curiosity in the Wolozin study is the virtual abolition of AD by statin treatment in women, in whom the reduction of prevalence was 96.3% (page 1442, upper left). The report that there is virtually no AD in statin-treated women would be at odds with general clinical experience, and does invoke Jick et al's suggestion that statin use may be associated with socioeconomic status and education, both of which are associated with lowered dementia risk.

Two recent reviews have addressed the use of statins to prevent AD. Zhou et al (Dement Geriatr Cogn Disord 2007; 23:194-201) [copy enclosed] performed a meta-analysis of studies of the effect of statin administration on dementia. While retrospective studies had suggested a reduced risk of AD in statin-treated patients, randomized, controlled clinical trials showed no reduction of risk. The British Association for Psychopharmacology's consensus statement also noted type 1a (randomized controlled trial) evidence of no effect of statins in the prevention of AD.(Burns et al, Journal of Psychopharmacology 2006; 20:732-755) They consider that the "considerable reduction in risk associated with [the Jick and Wolozin] studies could be caused by individuals receiving statins having other characteristics associated with a lower risk of dementia i.e. bias by indication. This bias seems more likely in dementia studies as other evidence suggests that more affluent individuals with higher educational achievement are more likely to request and receive statin therapy. In support of this a community cohort study found that every use of statins was not associated with the risk of dementia but current use of statins was associated with a reduced hazard ratio of 0.69 (Rea et al, 2005)." The authors also point out, in contrast to much of the cited effects of

cholesterol on AD biochemical pathways, that "low brain cholesterol concentrations may promote neurodegeneration."

In summary, it was not accepted that lowering cholesterol concentrations would prevent dementia prior to the priority date of this application, and this has not changed..

The examiner's argument when stripped to its basics seems to be: galanthamine is used to treat Alzheimer's disease; high cholesterol may increase Alzheimer's disease, statins reduce cholesterol, therefore it is obvious to use two routes used or suggested for treating Alzheimer's disease together to treat other cognitive dysfunction. As noted above, the second of these premises is not supported by the data. Even if it were, the argument requires a leap of faith rather than reason. Just because two treatments may be effective against a particular condition it does not make it obvious to combine them to treat that condition. One must consider what is known about the condition and how the treatments work to see whether they are likely to work together or to hinder each other. When one moves on from considering whether treatments should be combined for treating a condition other than the one for which they have been used hitherto, the leap into the dark becomes even greater. No reason has been given as to why either of the treatments discussed by the examiner would be expected to help with cognitive dysfunction other than that associated with Alzheimer's disease. There is absolutely no reason why one skilled in the art would have thought to do this. As noted above, prior thinking was that low cholesterol was good. Nothing in the art cited suggests that having achieved this desideratum one would need to treat it. Although references given in the present application indicate that there was some prior awareness that low cholesterol might not be all good, none indicated why this was the case or pointed towards the desirability of nicotinic allosteric potentiation as a way to treat it. However, that is what the present applicant found and based on this invented a way to treat the problem.. Nothing in the art points to this.

Submitted herewith are slides taken from Winblad et al Drugs Aging 2007; 24:56 - 71, Hamouda et al, Biochemistry 2006, 45:976-986 and Pediconi et al Neuroscience 128 (2004) 239-249. The first of these shows a surprising improvement in cognitive performance in patients receiving statins when galanthamine treatment was added. Total cholesterol values

did not differ significantly between statin-treated and untreated groups. Alzheimer disease patients receiving galantamine improved by $0.88 \pm .25$ (SE) points on the ADAS-cog after 5-6 months' treatment. In comparison Alzheimer disease patients receiving statins improved by $2.85 \pm .91$ points, significantly more than those not receiving statins. Deterioration in the statin-only and placebo-only groups did not differ significantly, consistent with the failure of statins to alter the development of dementia. The differential effects of galanthamine as a function of statin administration indicate that galanthamine had a substantial additional effect in statin-treated patients beyond that which occurred in Alzheimer patients. This additional effect is the predicted improvement of cognition in the presence of statins. The data obtained show the efficacy of the present invention and the surprising results it produces.

The second slide illustrates how cholesterol interacts with a nicotinic receptor and so provides confirmation of the applicant's original insight that cognitive problems associated with low cholesterol values might be alleviated by use of nicotinic allosteric potentiators .(and is an actual picture of the cholesterol location sketched in the schematic cartoon provided in the Response of January 10, 2006.)

The third slide shows that low cholesterol values reduces the number of nicotinic acetyl cholinesterase receptor sites on the surface of the cell. The applicant's insight lay in appreciation of the relationship of the clinical consequences of cholesterol depletion with nicotinic receptor function, and the substantial result of augmenting that receptor function. This slide depicts how this may occur. Nothing in the art points to her inventive insight or the practical application of it that forms the present invention.

It is submitted therefore that the art in no way teaches the treatment of cognitive dysfunction with galanthamine or any nicotinic allosteric potentiator, nicotine, a nicotinic agonist or a mixture thereof and that the claims submitted comply with 35 USC 103 and should be allowed and the withdrawn claims recombined.

An error in the response of January 10, 2006 has been noticed which the applicant wishes to correct. The first sentence of the third paragraph on page 9 says that there was a correlation between the change in cognitive tests and the percent change in serum LDL-cholesterol level in the Muldoon 2000 article. In fact, those two results were unrelated. The change in performance was significantly related to the post-treatment LDL-cholesterol level.

Thus, it seems that humans behave like the nicotinic receptors do in artificial reconstituted membranes. There appears to be an absolute requirement for a certain amount of cholesterol, below which functioning will be impaired

In view of the foregoing, it is submitted that this application is now in order for allowance and an early action to this end is respectfully solicited.

Respectfully submitted,

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